

Amendments to the Specification

Page 1, before the first paragraph, please insert the following paragraph:

This application is a national filing under 35 USC 371 of PCT/GB2003/002919, filed July 4, 2003 which claims priority from European Application 02255107.1, filed July 22, 2002.

Please replace the paragraph on page 9 which spans lines 18-29 with the following amended paragraph (the additions have been indicated by underlining):

The linker may be any group which links the polymer and the NCT agent and which does not effect the in vivo solubility or toxicity properties of the polymer-NAT conjugate. Such linkers include linear or branched C₁₋₁₅ alkyl which may be saturated or unsaturated, optionally substituted by carbonyl, amide, hydroxyl or halogen, such as methyl, ethyl, propyl, n-butyl, i-butyl, t-butyl, 1-methylbutyl and methylpentyl; and peptides, preferably 1-10 amino acids in length in which the amino acids may be further substituted with amino, thio, carboxyl, carboxamide or imidazole groups. Preferred peptides are Gly-Gly [SEQ ID NO: 1], Gly-Phe-Gly [SEQ ID NO: 2], Gly-Phe-Phe [SEQ ID NO: 3], Gly-Leu-Gly [SEQ ID NO: 4], Gly-Val-Ala [SEQ ID NO: 5], Gly-Phe-Ala [SEQ ID NO: 6], Gly-Leu-Phe [SEQ ID NO: 7], Gly-Leu-Ala [SEQ ID NO: 8], Ala-Val-Ala [SEQ ID NO: 9], Gly-Phe-Leu-Gly [SEQ ID NO: 10], Gly-Phe-Phe-Leu [SEQ ID NO: 11], Gly-Leu-Leu-Gly [SEQ ID NO: 12], Gly-Phe-Tyr-Ala [SEQ ID NO: 13], Gly-Phe-Gly-Phe [SEQ ID NO: 14], Ala-Gly-Val-Phe [SEQ ID NO: 15], Gly-Phe-Phe-Gly [SEQ ID NO: 16], Gly-Phe-Leu-Gly-Phe [SEQ ID NO: 17] and Gly-Gly-Phe-Leu-Gly-Phe [SEQ ID NO: 18]. Particularly preferred peptides are Gly-Gly [SEQ ID NO: 1] and Gly-Phe-Leu-Gly [SEQ ID NO: 10].

Please replace the paragraph which spans page 11 lines 29-31 through page 12 lines 1-3 with the following amended paragraph (the additions have been indicated by underlining):

Preferably, the polymer is a copolymer of N-(2-hydroxypropyl)methacrylamide (HPMA) and methacrylic acid; the linker is a peptide, such as Gly-Phe-Leu-Gly [SEQ ID NO: 10]; and the NAT agent is selected from o-carboranylalanine $B_{10}C_2H_2-CH_2CHCO_2NH_2$, carborane butamine $B_{10}C_2H_2-(CH_2)_3CHCO_2NH_2$, BPA (p-boronophenylalanine), B₁₂H₁₁SH (BSH) (mercaptoundecahydrododecacarborate), boronated porphyrins, BSH-glutathione disulfide, and water soluble tetracarbonylphenylporphyrin eg. NiTCP.

Please replace the paragraph on page 12 which spans lines 5-13 with the following amended paragraph (the additions have been indicated by underlining):

Particularly preferred conjugates are:

HPMA-co-MA-Gly-Phe-Leu-Gly-BSH [SEQ ID NO: 10]

HPMA-co-MA-Gly-BPA-Leu-Gly-BPA [SEQ ID NO: 10]

HPMA-co-MA-Gly-BPA-Leu-Gly-Gly-BPA [SEQ ID NO: 19]

HPMA-co-MA-Gly-Phe-Leu-Gly-Carborane butamine ($B_{10}C_2H_{11}(CH_2)_3CHCO_2NH_2$) [SEQ ID NO: 10]

HPMA-co-MA-Gly-BPA-Leu-Gly-Carborane butamine ($B_{12}H_{11}-(CH_2)_3CHCO_2NH_2$) [SEQ ID NO: 10]

HPMA-co-MA-Gly-Phe-Leu Gly-CuTCPH [SEQ ID NO: 10]

HPMA-co-MA-Gly-Phe-Leu-Gly-CuTCPHBr [SEQ ID NO: 10]

Please replace the paragraph on page 14 which spans lines 19-24 with the following amended paragraph (the additions have been indicated by underlining):

A preferred conjugate of this type is HPMA-co-MA-[Gly-Phe-Leu-Gly-BSH)(Gly-Phe-Leu-Gly-Y)], where Y is the anticancer agent [SEQ ID NO: 20], for example:

HPMA-co-MA [(Gly-Phe-Leu-Gly-BSH)(Gly-Phe-Leu-Gly Doxorubicin)] [SEQ ID NO: 20]

HPMA-co-MA [(Gly-Phe-Leu-Gly-BSH)(Gly-Phe-Leu-Gly Ellipticin)] [SEQ ID NO: 20]

HPMA-co-MA [Gly-Phe-Leu-Gly-BSH)(Gly-Phe-Leu-Gly Cisplatin)] [SEQ ID NO: 20]

Please replace the paragraph on page 18 which spans lines 1-12 with the following amended paragraph (the additions have been indicated by underlining):

The polymer-NAT conjugates of examples 1 and 2 only differ in their peptide linkers. The polymer-NAT conjugate of example 1 has the peptide linker Gly-Phe-Leu-Gly [SEQ ID NO: 10] which is enzymatically degraded in the lisosomal compartment of a cell to release the BPA whereas the polymer-NAT conjugate of example 2 has the peptide linker “Gly-Gly” [SEQ ID NO: 1] which is not degraded leaving the entire molecule intact. The biodegradable polymer is able to release the boron-carrying molecule into the cytoplasm and has the opportunity to diffuse into the heart of cellular organelles and most importantly into the nucleus. In BNAT, the closer the boron carrier molecule is to the DNA the more effective the cell kill. However, with the non-degradeable polymer-NAT conjugate, the molecule remains intact and is unable to leave the cell once it has been internalised. This allows a build up of a very high concentration of the boronated ploymer in a cell via multiple doses which otherwise may not be possible due to systemic toxicity of the boronated polymer.

Please replace the paragraph on page 21 which spans lines 3-18 with the following amended paragraph (the additions have been indicated by underlining):

Example 5

Preparation of poly(HPMA-co-MA-Gly-Phe-Leu-Gly-BSMe)-Gly-Phe-Leu-Gly-Paclitaxel (PP405)
[SEQ ID NO: 20]

Powdered poly(HPMA-co-MA-GFLG-ONp) (2.15 g, 45.6 μ mol) was placed in a dried flask which was sealed with a septum and flushed out with argon. Anhydrous DMSO (22 mL) was added and the mixture was stirred until all the material had dissolved. BSMel (0.146 g, 366 μ mol) was added. When all the solid had dissolved, triethylamine (52 μ L, 366 μ mol) was added causing the solution to become yellow. The solution was stirred at 20-22°C (oil bath temperature) under argon for 5 h. Paclitaxel (0.313 g, 366 μ mol) and 4-dimethylaminopyridine catalyst (0.015 g, 123 μ mol) were added. After stirring overnight at 20-22°C, 3-amino-1-propanol (35 μ L, 456 μ mol) was added and the solution was stirred for a further 4h. The solution was slowly poured into stirred diethyl ether (500ml) and the solvent was decanted off the sticky precipitate. The yellowish solid was triturated with further portions of diethyl ether until it was no longer sticky. Residual solvent was evaporated in vacuo. Yield 2.44 g (98%).

Please replace the paragraph on page 22 which spans lines 4-18 with the following amended paragraph (the additions have been indicated by underlining):

Example 6

Preparation of poly(HPMA-co-MA-Gly-Phe-Leu-Gly-BSMel)Gly-Phe-Leu-Gly-Doxorubicin (PP406) [SEQ ID NO: 20]

Powdered poly(HPMA-co-MA-GFLG-ONp) (2.15 g, 45.6 μ mol) was placed in a dried flask which was sealed with a septum and flushed out with argon. Anhydrous DMSO (22 mL) was added and the mixture was stirred until all the material had dissolved. BSMel (0.146 g, 366 μ mol) was added. When all the solid had dissolved, triethylamine (52 μ L, 366 μ mol) was added. The solution was stirred at 20-22°C (oil bath temperature) under argon for 5h. Doxorubicin hydrochloride (0.212 g, 366 μ mol) and triethylamine (52 μ L, 366 μ mol) were added. After stirring overnight at 20-22°C, 3-amino-1-propanol (35 μ L, 456 μ mol) was added and the solution was stirred for a further 4 h. The

solution was slowly poured into stirred diethyl ether (500 mL) and the solvent was decanted off the sticky precipitate. The red solid was triturated with further portions of diethyl ether until it was no longer sticky. Residual solvent was evaporated in vacuo. Yield 2.55g (105%).